REMARKS

By this amendment, claims 10 and 11 are cancelled and new claims 12-18 are added. Support for new independent claim 12 is found, *inter alia,* in claim 1 as amended under PCT Article 19 and in original claim 3. New claims 13-17 are respectively supported by original claims 2 and 4-7. Finally, support for claim 18 can be found in the paragraph bridging pages 9 and 10 of the specification and in original claim 11. Claims 1-9 and 12-18 are presented for further examination.

Applicants acknowledge with appreciation the indication by the examiner that the a copy of the priority document has not yet been received from the International Bureau. Accordingly, Applicants will submit a copy of the priority document in a future communication.

The rejection of claims 1-11 under 35 U.S.C. § 103(a) as obvious over Kawai, EP 0 703 450 A10, either alone or in view of Ryan, WO 97/25303 is respectfully traversed.

According to the present invention, Applicants have surprisingly discovered that the amount of 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) in fluoromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether (crude sevoflurane) can be dramatically reduced by contacting crude sevoflurane containing not greater than about 0.25 wt.% of at least HFIP with a basic aqueous solution. By contacting crude sevoflurane having this critical amount of HFIP with a basic aqueous solution, the HFIP can be removed from the crude sevoflurane. As recited in claim 1, the basic aqueous solution contains a basic substance in an amount such that a chemical equivalent ratio of the basic substance to HFIP is not less than 1.

As acknowledged in the Office Action, Kawai does not teach the amount of HFIP in the crude sevoflurane. Moreover, the Office Action concedes that according to the teaching of Kawai, the amount of HFIP is not critical.

Furthermore, Kawai does not teach the claimed chemical equivalent ratio of the basic substance to HFIP. These deficiencies of Kawai are not remedied by Ryan.

The combination of Ryan and Kawai does not reasonably suggest contacting crude sevoflurane having a critical amount of HFIP (≤0.25 wt.%) with a basic aqueous solution to remove HFIP from the crude sevoflurane. Ryan discloses a process for the production of sevoflurane. As noted in the Office Action dated March 27, 2002, Ryan further discloses that the reaction between bis(fluoromethyl)ether and HFIP can be carried out to result in complete conversion of the HFIP. Based on the teaching of Ryan, one would not have been motivated to remove HFIP from an already HFIP-free sevoflurane product. As disclosed by Ryan at page 2, lines 29-31, "[c]arrying out the reaction with complete conversion of the [HFIP] obviates the need to recover and recycle unreacted alcohol."

Moreover, even assuming *arguendo* that a *prima facie* case of obviousness had been made out, it would be effectively rebutted by the unexpected, superior results achieved by the critical ranges associated with the claimed process as set forth in the current application as well as in Applicants' Declaration submitted with the Reply dated September 26, 2002. See In re Margolis, 228 USPQ 940 (Fed. Cir. 1986).

Example 3 of the application establishes that the HFIP content in crude sevoflurane is dramatically reduced from 0.25 wt% to an amount less than the detection limit of 1 ppm (i.e., 0.0001 wt%) by the alkali washing. One with skill in the art would appreciated that, if the initial HFIP content in the crude sevoflurane is less than 0.25 wt.%, the post-washing HFIP content would also be less than the detection limit of 1 ppm. This is an unexpected and surprising result in which the HFIP content is reduced to less than 1/2,500th of the original content, and is further confirmed by Experiment 3 of the Declaration.

Both Example 3 and Experiment 3 are commensurate with the scope of the claims and show that by causing crude sevoflurane containing not greater than about 0.25 wt.% HFIP to contact a basic aqueous solution, the HFIP can be removed from the crude sevoflurane. The cited prior art does not teach or suggest a method of removing HFIP from crude sevoflurane that results in such a dramatic reduction in the HFIP concentration.

Ryan teaches an already HFIP-free sevoflurane. Kawai teaches the purification of crude sevoflurane but fails to achieve the results of the present invention. To demonstrate this, Applicants produced crude sevoflurane in accordance with Example 1 of Kawai and washed this material with 4% sodium hydroxide aqueous solution in accordance with Example 6 of Kawai. The initial HFIP content in the crude sevoflurane produced according to the process of Kawai was 4.91 wt.% (see Experiment 1 of the Declaration and the results of Run 1). After washing this crude sevoflurane sample with the 4% sodium hydroxide solution, the HFIP content was reduced to 0.05 wt.%, which corresponds to a reduction of only about 1/100th of the original content (see Experiment 2 of the Declaration).

The superior and unexpected results achieved using the process of the present invention effectively rebut any *prima facie* case of obviousness based on Kawai and Ryan. Further, in contrast to the assertion made in the Office Action, the Declaration does set forth facts that directly compare the claimed invention and the closest prior art.

Example 3 of the invention, which was confirmed in Experiment 3 of the Declaration, is commensurate with the scope of the claims and demonstrates that the HFIP content is reduced from 0.25 wt.% to less than 1/2,500th of that value as a result of alkali washing. The Declaration directly compares this result with the result of using the process of Kawai.

Example 6 of Kawai, which was identified in the Office Action dated March 27, 2002 to be the closest prior art of record, shows a reduction in the HFIP content of to only about 1/100th of the pre-washing value.

In this direct comparison between the instant invention and the closest prior art of record, Applicants have demonstrated the superior and unexpected results that the amount of the reduction of the HFIP content by alkali washing is unexpectedly much greater in the case in which the HFIP content of the crude sevoflurane before the alkali washing is 0.25 wt%, as in Example 3 of instant specification, as compared with the case in which the HFIP content of the crude sevoflurane before the alkali washing is 4.91 wt%, as in Example 6 of Kawai.

Notably, the fractional reduction achieved using the process of the claimed invention (1/2,500) is more than an order of magnitude greater than the fractional reduction achieved using the process of Kawai (1/100). In achieving this reduction, Applicants have also shown that the amount of HFIP in crude sevoflurane is critical in obtaining high purity sevoflurane, and the effect of the claimed process in removing un-reacted HFIP depends on the initial concentration of un-reacted HFIP.

New claims 12-18 recite that the HFIP content in the crude sevoflurane is less than about 1 wt.% and further require that the crude sevoflurane is contacted with a basic aqueous solution at a temperature ranging from 0 to 60°C. Because none of the cited reference teaches or suggests the criticality of the HFIP content in the crude sevoflurane, these claims are believed to be patentable at least for the reasons discussed above with respect to claims 1-9.

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #038788.48236).

Respectfully submitted,

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